Applicants: James Binley et al.
Serial No.: 10/780,993
Filed: January 18, 2004
Exhibit 7

Office Action Summary	Application No.	Applicant(s)	
	10/489,040	MOORE ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *112-134* is/are pending in the application.

4a) Of the above claim(s) *114 and 127-134* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *112,113 and 115-126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/_ _ _ 3/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

The Office acknowledges the receipt of Applicant's Election and Amendment, filed on 9 March 2006. Claims 1-111 have been canceled. Claims 112-134 are newly added. Therefore, claims 112-134 are pending.

Election/Restrictions

Applicant elects Group IV, claims 5-9, 14, and 15, with traverse. Because applicant did not distinctly and specifically point out any supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 112, 113, and 115-126 are drawn to the elected invention. Claims 114 and 127-134 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention/species. Should the elected product claims be allowable, Applicants are entitled to the rejoinder of the process claims with the product claims under *In re Ochiai* and *In re Brouwer*. See M.P.E.P. §821.04.

Accordingly, Claims 112, 113, and 115-126 are examined.

Sequence Compliance

The specification is objected to for failing to adhere to the requirements of the sequence rules. Applicant must append SEQ ID Nos. to all mentions of specific sequences in the specification and the claims. See 37 CFR § 1.821(d). Full compliance is required in response to this Office Action. A reply that fails to comply will

be considered to be non-responsive and may result in ABANDONMENT of this application.

Information Disclosure Statement

An initialed and dated copy of each of Applicant's IDS form 1449, filed on 13 December 2004 and 9 March 2006, respectively, is attached to the instant Office action.

It is noted that there is a typographical error in the IDS effectively filed on 13 December 2004. The document number for Exh No. 7 should be 2003/0052839 instead of 2002/0052839.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because only one inventor signed.

Claim Objections

Claim 122 is objected to because a comma is missing behind the word "Q590." Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 112 and 121 rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 112, it is unclear whether the limitation "consecutive amino acids" means the same as a peptide or amino acids arranged in a way different from a protein peptide.

In claim 121, the recitation "position A" is indefinite. It is unclear what "A" stands for.

Clarification and/or correction are required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 112, 113, and 115-126 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The M.P.E.P. states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

M.P.E.P. § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

M.P.E.P. § 2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See M.P.E.P. § 2163. Although the M.P.E.P. does not define what constitutes a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention*. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." M.P.E.P. §2163.

In the instant case, the claims are directed to a polypeptide comprising the amino acid sequence of HIV-1 gp120 and HIV-1 gp41, wherein (i) the gp41 sequence further comprises one or more mutations in its N-terminal helix, and (ii) the gp120 and gp41 are bound to one another by a disulfide bond between a cysteine residue in gp120 and a cysteine residue in gp41. The limitation on the gp41 mutation encompasses all mutated

sequences, structural or functional homologs, and so forth. Thus, the claims are drawn to a genus of proteins that is defined only by functional reduction.

The only factor present is the functional characteristic of the ectodomain of HIV envelope protein. There is not even an identification of any particular portion of the structure that must be conserved. The specification only provides description for a number of mutations at specific positions (pages 39, ¶ 152).

As stated *supra*, the M.P.E.P. states that written description for a genus can be achieved by a representative number of species within a broad genus. Claim 112 is broadly generic to mutations at all possible residue positions, from about 512 to about 878, encompassed by the claims. The possible variations are enormous in comparison to the 13 specific mutations described in the specification. Since the M.P.E.P. states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." M.P.E.P. §2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the gp41 mutant variants beyond those disclosed in the examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of mutations at the other 300 or so positions.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states: "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* on page 1116).

As discussed above, the skilled artisan cannot envision the detailed chemical structure and function of the encompassed genus of undefined modified peptides. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or synthesis. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of cloning or isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Therefore, only the mutants at 13 positions have been described.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483, claims directed to mammalian FGF's were found to be unpatentable due to lack of written descriptions for that broad class. The specification provided only the bovine sequence.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984)

(affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

The patent law requires that a patent contain a written description of a claimed invention independent of the requirements to enable one skilled in the art to make and use the invention. See e.g., *Invitrogen Corp. v. Clontech Labs, Inc.*, 429 F.3d 1052, 1071 n.17 (Fed. Cir. 2005) ("written description is distinct from the enablement requirement"); *Capon v. Eshhar*, 418 F.3d 1349, 1360 (Fed. Cir. 2005) ("although the legal criteria of enablement and written description are related and are often met by the same disclosure, they serve discrete legal requirements").

Therefore, claims 112, 113, and 115-126 do not meet the written description provision of 35 U.S.C. §112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variable. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 112, 113, 115, 116, 119, 121, and 124 are rejected under 35 U.S.C. §102(b) as being anticipated by Binley *et al.* (2000, Jan, listed in IDS filed on 19 July 2004).

The instant claims are drawn to a protein comprising a first polypeptide which comprises consecutive amino acids encoding a modified gp120 of a HIV-1 isolate, which modified gp120 includes a first cysteine introduced by a mutation, and a second polypeptide which comprises consecutive amino acids encoding a modified gp41 ectodomain of such HIV-1 isolate, which modified gp41 ectodomain includes a second cysteine introduced by a mutation, wherein (i) the second polypeptide further comprises one or more mutations in its N-terminal helix, and (ii) the first and second polypeptides are bound to one another by a disulfide bond between the first cysteine and the second cysteine; a stable HIV-1 pre-fusion envelope glycoprotein trimeric complex comprising the protein as a monomeric unit; and a composition comprising the trimeric complex and a pharmaceutically acceptable carrier.

Binley *et al.* teaches a recombinant HIV-1 envelope glycoprotein complex stabilized by an intermolecular disulfide bond between the gp120 and gp41 subunits, which mimics the monomeric unit of the trimeric complex of HIV envelope glycoprotein (Title and Abstract). Specifically, Binley *et al.* teaches a group of cysteine mutants of

HIV subtype B, strain JR-FL, gp140 (p. 628, left column, ¶ 5, right column, last ¶, and Fig. 7), including quadruple cysteine substitutions such that the gp41 ectodomain comprises one more mutation in the N-terminal helix. Binley *et al.* further teaches mutated furin recognition sequence by amino acid substitution (p. 628, left column, ¶ 4).

Thus, Binley *et al.* clearly anticipates claims 112, 113, 115, 116, 119, 121, and 124.

Claims 112, 113, 115-121 and 124-126 are rejected under 35 U.S.C. §102(e) as being anticipated by Binley *et al.* (US 2003/0052839, referred to as PGPub'839, listed in IDS filed on 19 July 2004).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. §102(e). This rejection under 35 U.S.C. §102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The instant invention is further limited to the glycosylation sites and a disulfide bond between cysteine residues introduced by mutations A492C and T596C.

PGPub'839 teaches an isolated HIV-1JR-FL envelope glycoprotein complex comprising a gp120 and gp41 bound to one another by a disulfide bond between a cysteine residue introduced by an A492C mutation into gp120 and a cysteine residue introduced by a T596C mutation into gp41 (¶127, ¶129, and ¶130), wherein the gp41

further comprises a mutation at the N-terminal helix, P600C (¶275). The modified gp120 further comprises a mutated furin cleavage site (¶67) and is characterized by the presence of one or more canonical glycoylation sites not present in wild type gp120, or by the absence of one or more canonical glycosylation sites present in wild type gp120 (¶114-115). PGPub'839 further teaches a trimer comprising three identical modified proteins of gp120 bound to gp41, a composition comprising an adjuvant and the HIV envelope complex or the trimer (Claims).

Thus, the instant invention is anticipated by PGPub'839.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 112, 113, 115, 116, 119, and 121-124 are rejected under 35 U.S.C. §103(a) as being unpatentable over Binley *et al.* (2000, Jan, listed in IDS filed on 19 July 2004) in view of Chen *et al.* (1993).

The instant invention is further limited to a mutation of the second polypeptide located at position I559, with reference to the HIV-1 isolate HIV-1 strain JR-FL.

The relevance of Binley *et al.* is set forth above.

Binley *et al.* does not teach the additional mutation in the second polypeptide at the indicated position.

Chen *et al.* teach substitution of Ile-559 with Pro residue to disrupt the N-terminal helix (p. 3615, right column, ¶3) and disclose that the I559P mutation does not affect Env protein oligomerization but affect virus infectivity (p. 3618, left column, ¶3, and Table 1).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the HIV gp120 monomer of Binley *et al.* by adding mutation I559P in gp41 such that the infectivity of the peptide is reduced. One having ordinary skill in the art would have been motivated to do this to obtain safety for these immunogenic peptides without changing the overall structure, so as to maintain the antigenic properties, as suggested by Chen *et al.*

Thus, claims 112, 113, 115, 116, 119, and 121-124 are obvious over Binley *et al.* in view of Chen *et al.*

Claims 112, 113, 115, 116, 119-121, and 124 are rejected under 35 U.S.C. §103(a) as being unpatentable over Binley *et al.* (2000, Jan) in view of Sanders *et al.* (2000, Jun).

The instant invention is further limited to the absence of canonical glycosylation sites present in wild type HIV gp120.

The relevance of Binley *et al.* is set forth above.

Binley *et al.* does not teach the absence of canonical glycosylation sites present in wild type HIV gp120.

Sanders *et al.* describes a trimeric HIV envelope glycoprotein complex containing monomers of gp140 that are stabilized by an intermolecular disulfide bond between gp120 and the gp41 ectodomain (Abstract and Introduction). Specifically, Sanders *et al.* describes absence of canonical glycosylation sites present in wild type gp120 (p. 5093, right ¶; p. 5098, right column, ¶2) and mutation of the REKR cleavage site for furin proteases at the gp120 C terminus (p. 5098, left column, ¶3).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the HIV gp120 monomer of Binley *et al.* by removing the canonical glycosylation sites present in wild type gp120 such that the carbohydrate content is further reduced. One having ordinary skill in the art would have been motivated to do this to obtain favorable antigenic properties for these peptides, as suggested by Sanders *et al.*

Thus, claims 112, 113, 115, 116, 119-121, and 124 are obvious over Binley *et al.* in view of Sanders *et al.*

Remarks

No claim is allowable.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D., whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902.

Louise Humphrey, Ph.D.
Assistant Patent Examiner
13 April 2006

JEFFREY STUCKER
PRIMARY EXAMINER

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Please find below and/or attached an Office communication concerning this application or proceeding.